FORM PTO-1390 (REV 10-94) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		11669 99USWO
		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) unknown 09/937498
INTERNATIONAL APPLICATION NO. PCT/IB00/00608	INTERNATIONAL FILING DATE 31 March 2000	PRIORITY DATE CLAIMED 2 April 1999

TITLE OF INVENTION

STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR

APPLICANT(S) FOR DO/EO/US

MORITA et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [x] is transmitted herewith (required only if not transmitted by the International Bureau)
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2))

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau)
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))

9. [X] An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4))

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5))

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment

14. [ ] A substitute specification

15. [ ] A change of power of attorney and/or address letter

16. [x] Other items or information: International Publication Page, Preliminary Amendment, Abstract, Marked-up Copy, Form PCT/RO/101, Form PCT/ISA/210, Form PCT/IB/304, Form PCT/IPEA/408, 1 Sheet of Formal Drawings

[redacted]

JC08 Rec'd PCT/PTO 25 SEP 2001

U.S. APPLICATION NO (If known, see 37 C F R 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
unknown 09/937498	PCT/IB00/00608	11669.99USWO

17. [X] The following fees are submitted.

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):

Search Report has been prepared by the EPO or JPO **$860.00**

International preliminary examination fee paid to USPTO (37 CFR 1 492(a)(1)) **$690.00**

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$710.00**

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO **$1000.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =				**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				**$**	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	16	-20 =	0	X **$18.00**	**$0.00**
Independent claims	4	-3 =	1	X **$80.00**	**$80.00**
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ **$260.00**	**$**
TOTAL OF ABOVE CALCULATIONS =					**$940.00**
Reduction by 1/2 for filing by small entity, if applicable Small entity status is claimed pursuant to 37 CFR 1 27					**$**
SUBTOTAL =					**$940.00**
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f).				+	**$**
TOTAL NATIONAL FEE =					**$940.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40 00 per property				+	**$**
TOTAL FEES ENCLOSED =					**$940.00**
				Amount to be: refunded	**$**
				charged	**$**

a. [X] Check(s) in the amount of $940.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No 13-2725

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
Natalie D Kaievitch
MERCHANT & GOULD
P.O. Box 2903
Minneapolis, MN 55402-0903

SIGNATURE Natalie D. Kadievitch

NAME Natalie D Kadievitch

REGISTRATION NUMBER 34,196

[redacted]

S/N unknown PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	MORITA et al.	Serial No.:	unknown
Filed:	concurrent herewith	Docket No.:	11669.99USWO
Title:	STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR		

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number EL921133625US
Date of Deposit. 25 September 2001
I hereby certify that this correspondence is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D C 20231

By: Omesh Singh
Name. Omesh Singh

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment.

IN THE ABSTRACT

Insert the attached Abstract page into the application as the last page thereof.

IN THE SPECIFICATION

A courtesy copy of the present specification is enclosed herewith. However, the World Intellectual Property Office (WIPO) copy should be relied upon if it is already in the U.S. Patent Office.

IN THE CLAIMS

Please amend claims 3-4 as follows:

3. (Amended) A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4. (Amended) A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein said polyvalent metal ions are zinc ions or aluminum ions.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 3 and 4.

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract is typed on a separate page as required by U.S. practice.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Marked-up Copy".

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Natalie D Kadievitch (Reg. No. 34,196), at (612) 336.4706.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Dated: 25 September 2001

By Natalie D. Kadievitch
Natalie D. Kadievitch
Reg. No. 34,196

NDK:hjh

ABSTRACT

The invention has the purpose of offering a storage container wherein flocculation and nebulation of hGH does not occur during storage of an hGH solution. A rubber stopper is formed of rubber such that when one such rubber stopper is immersed in 1 ml of a buffer solution having a pH of approximately 5.5 to 6.5 and containing a surfactant, stored while shaking for one week at a temperature of 25 °C, then the metal ion elution rate in the buffer solution is measured using atomic absorption spectrophotometry, the elution rate of polyvalent metal ions is 50 ppm or less.

MARKED-UP COPY

3. A storage container for a weakly acidic solution formulation in accordance with [either claim 1 or 2,] claim 1, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4. A storage container for a weakly acidic solution formulation in accordance with [any one of claims 1-3,] claim 1, wherein said polyvalent metal ions are zinc ions or aluminum ions.

09/937498
JC03 Rec'd PCT/PTO 25 SEP 2001

Storage Container for Weakly Acidic Solution Formulation Containing Human Growth Hormone, Injection Cartridge Therefor and Storage Method Therefor

TECHNICAL FIELD

The present invention relates to a storage container for a weakly acidic solution formulation containing human growth hormone, an injection cartridge therefor and a storage method therefor

BACKGROUND ART

Human growth hormone (sometimes referred to as "hGH" below) is a single-chain polypeptide hormone composed of 191 amino acid residues. hGH can undergo decomposition by a number of routes, for example, by deamidation, flocculation, precipitation, oxidation of methionine residues and proteolysis. In order to avoid such decomposition reactions, hGH has conventionally been formulated and sold in freeze-dried form. However, recent years have seen a rising demand for the development of solution formulations for clinical reasons such as in order to improve the compliance of patients by simplifying the method of use, and various such formulations have been announced (see, e.g, PCT Application, Japanese-Language Publication No. Hei 7-809719; Japanese Patent Application, First Publication No. Hei 8-92125).

These solution formulations employ a weakly acidic buffer solution with a pH (pH 6-7) slightly less than the weakly alkaline physiological pH, pH 7-7 5, which has been conventionally employed in freeze-dried formulations This is because slight alkalinity may cause deamidation of the hGH during storage as a solution However, with slight acidity of pH 6-7, hGH may tend to precipitate, so that the addition of surfactants has been necessitated for long-term storage Additionally, the present inventors have observed that even when surfactants are added, precipitation or nebulation of the hGH can occur during long-term storage of the hGH solution depending on the conditions, and the cause of this phenomenon has conventionally been completely unexplained

On the other hand, since the rubber stoppers or rubber plungers used in injection-type solution formulations are in contact with the solution for a long time in comparison to the case where used in the container of a freeze-dried solution, problems in quality caused by the rubber stopper material can often occur Whereas examples of problems associated with rubber stoppers include contaminants adhering to the rubber stopper, coring and sticking, a particular problem for solution formulations is the effect of elutes from the rubber stopper on the quality of the pharmaceutical

agent. Rubber stoppers have very complicated properties both chemically and physically, and various types of elute substances from rubber stoppers are known These are, for example, reported by L Gramiccioni *et al* (*Chromatographia*, 28 ('89) 545-550). However, it has yet to be examined which of the elute substances from rubber stoppers have what type of effects on a hGH solution formulation, particularly weakly acidic solution formulations, and there have been no such reports as far as the inventors are aware.

Therefore, the present inventors performed diligent research in this regard, as a result of which they discovered that the formulation container, particularly the material of the rubber stopper is an important factor in the stable storage of hGH solution formulations. That is, they discovered that metal ions dissolve from the rubber stopper during long-term storage and form conjugates with the hGH. Based on this discovery, they found that it is necessary to use a rubber stopper in which the elution of metal ions (especially zinc ions and/or aluminum ions) under certain conditions is below a standard amount in order to prevent degradations of the quality of the hGH solution formulation, thereby arriving at the present invention.

DISCLOSURE OF THE INVENTION

Specifically, the storage container for a weakly acidic solution formulation containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening; and a second sealing member provided in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the

first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the elution rate of polyvalent metal ions is 20 ppm or less

A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the polyvalent metal ions are zinc ions or aluminum ions.

An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening, having a thickness such as to be capable of being punctured by a syringe needle; and a second sealing member provided in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5 5-6 5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution

containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less

A method for storing a weakly acidic solution containing human growth hormone according to the present invention comprises steps of preparing a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; providing a rubber stopper in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming a space with the first sealing member; filling the space with the weakly acidic solution formulation containing human growth hormone, and sealing the first opening with a cap. The rubber stopper is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a rubber stopper is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

A method for storing a weakly acidic solution containing human growth hormone according to another mode of the present invention is such that a polyvalent metal ion chelating agent is added to the weakly acidic solution formulation containing a human growth hormone

The terminology such as "buffer solution containing a surfactant" used in the present specification is defined as follows. "Buffer solution containing a surfactant" refers to a solution containing a citric acid-type, phosphoric acid-type, glycine-type or tris-type buffer, an isotonic agent such as sodium chloride, a surfactant such as Polysorbate 80, Polysorbate 20 or Poloxamer 188, and optionally, other preservatives and the like as needed. Polysorbate 20, Poloxamer 188 and the like are preferred as surfactants

"Rubber stopper or rubber plunger" refers to a rubber stopper for a syringe vial or a plunger used in a cartridge for a convenience-type syringe formulation. That is, a rubber stopper is a sealing plug composed of rubber used for an antiseptic seal after a vial container is filled with hGH. A rubber plunger is a sealing plug composed of rubber used for an antiseptic seal in an hGH solution-filled cartridge used in hGH administration devices

"hGH" refers to human growth hormone which was brought into practice almost 20 years ago as a treatment for pituitary dwarfism, of which various medical formulations are commercially available In the present invention, hGH includes not only hGH proteins from the human pituitary gland (191 amino acids, molecular weight approximately 22,000), but also to human growth hormone equivalents having biologically specific biological activity (e.g. substitution modifications, addition modifications, deletion modifications) Here, biological activity specific to hGH refers mainly to overall growth accelerating activity for causing all human tissues (especially bones) except for the brain to grow mainly during the developmental period, including the effects of accelerating production of bones and cartilage by IGF-I induction, promotion of amino acid intake to cells and protein synthesis, suppression of protein decomposition, promotion of neutral fat metabolism, promotion of sugar metabolism and promotion of electrolyte retention.

"Weakly acidic solution formulation containing hGH" refers to a solution formulation having a buffer with a pH of 5.5-7, and containing hGH as an active ingredient The appropriate pH range for such an hGH solution formulation is 5.5-7 0, and has been reported to be more advantageously 6.0 (PCT Application, Japanese-Language Publication No. Hei 7-509719).

"Storage container" refers to a fluid storage container such as a vial or cartridge for a syringe as commonly used in the field of pharmaceuticals.

According to the storage container for a weakly acidic solution formulation containing human growth hormone, injection cartridge therefor and storage method therefor of the present invention employing this type of structure, low levels of nebulation preferably, no nebulation is observed in the storage container containing human growth hormone, thus making it possible to offer an hGH solution formulation which is physically and chemically stable.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a side view showing a portion of a storage container according to the present invention in cross-section.

Fig. 2 is a perspective view showing the state of use of the storage container shown in Fig. 1.

BEST MODE FOR CARRYING OUT THE INVENTION

Herebelow, a mode for carrying out the present invention shall be described with reference to the drawings. Fig. 1 shows a storage container according to the present invention The storage container 10 has a roughly cylindrical container body

12 The container body 12 forms an internal cavity 14 this internal cavity 14 being open at the openings 16, 18 at the ends thereof. In the present embodiment, one end of the container body 12 has a smaller diameter to form a mouth portion 20 The mouth portion 20 has a thin rubber cap 22 and a metallic cap 24 covering this rubber cap 22 As shown in the drawings, these caps 22 and 24 are attached by pressing the cylindrical portion of the metallic cap 24 and the end portion of the tubular portion toward the mouth portion 20 and deforming it. The metallic cap 24 has an opening 26 opposing the opening 16 on roughly the central axis of the container body, such that by passing a needle into this opening 26 and through the rubber cap 22, it is possible to withdraw fluid from the inside.

In the internal cavity 14 of the container body 12, a roughly cylindrical rubber stopper 28 or rubber plunger is inserted from the opening 18 on the other side The rubber stopper 28 has a slightly larger outer diameter than the inner diameter of the internal cavity 14 of the container body when in a state of withdrawal from the container body 12 Consequently, when the rubber stopper 28 is in a state of insertion into the internal cavity 14 of the container body 14, a continuous seal is formed between the inner wall 30 forming this internal cavity 14 and the outer circumferential surface of the rubber stopper 28, as a result of which an enclosed chamber 32 is formed between the rubber cap 26 and the rubber stopper 28, and a liquid, i.e human growth hormone solution (weakly acidic solution formulation containing human growth hormone) 34 can be accommodated in this chamber 32.

When sealing human growth hormone solution 34 into the container body 12, the rubber stopper 28 is inserted from the opening 18 with the caps 26 and 28 unattached to the opening 16. Next, human growth hormone solution 34 is injected into the container body 12 from the opening 16 Finally, this opening 16 is covered with the rubber cap 22 and metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal Alternatively, the opening 16 is covered with the rubber cap 22 and the metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal. Next, the human growth hormone solution 34 is injected into the container body 12 through the opening 18. Finally, the rubber stopper 28 is inserted from the opening 18 while compressing to deform.

The human growth hormone solution 34 contained in the storage container 12 having this type of structure is, for example, injected into a patient using the syringe device (administration device) 40 of Fig. 2 offered under the trade name "Pen 100S" from Disetronic. This syringe device 40 is composed of a holder 42 for accommodating

the storage container 10 and an actuator 44 coupled to the rear end of this holder 42. Upon use, the storage container 10 is inserted into the holder 42 and the actuator is fitted to the rear end of this holder 42. Additionally, a cap 46 is attached to the front end of the holder 42. This cap 46 is provided with a needle 48 on an end surface, the two tips of this needle 48 protruding respectively from the inside end surface and outside end surface, the end of the needle 48 protruding from the inner end surface puncturing the rubber cap 22. In this state, the actuator 44 is operated, and the rubber stopper 28 of the storage container 12 is pressed. As a result, the human growth hormone solution 34 inside the storage container is delivered through the needle 48.

Herebelow, the rubber stopper of the storage container 12 shall be explained in detail. There are no restrictions as to the material of the rubber stopper as long as it is a material capable of being used in rubber stoppers for medical purposes. Butyl rubber, butyl chloride rubber and butadiene rubber are known as basic elastomers, and any of these may be used. Additionally, while the rubber stopper (or plunger) is used in combination with a vial and injection cartridge, their material and shape are not particularly restricted. Aside from glass which is commonly used, it is also possible to use, for example, synthetic resins such as polypropylene.

A rubber stopper suitable for the solution storage container of the present invention is most preferably selected by the following experiments.

(1) A buffer solution (pH 6) containing a surfactant is prepared, and 1 ml is put into a glass vial. The above-mentioned solution may optionally include isotonics, stabilizers, preservatives, anti-oxidants, solubilizers and excipients as appropriate. The test conditions may be changed according to the composition, storage conditions and method of use of the hGH solution formulation which is to be used, but in view of the purpose of strictly evaluating the amount of elutes from the rubber stopper, it is undesirable to add agents such as chelating agents which may have an effect on the metal ions.

(2) A single rubber stopper (approximately 1 g) is immersed in the above-described vial, and stored while shaking at 25 °C for one week.

(3) The amount of metal ions which have dissolved into the buffer solution is measured by atomic absorption spectrophotometry.

(4) Rubber stoppers having an elution rate of 50 ppm or less of polyvalent metal ions, particularly zinc and/or aluminum are selected. Preferably, those with an elution rate of zinc and/or aluminum ions of 20 ppm or less per rubber stopper under the above-given conditions are chosen.

(5) If the rubber stopper material fails to reach the above standards, it can be

modified or treated to provide it with properties suitable for the storage container of the present invention by means of surface treatment or the like. For example, by coating the rubber stopper with a fluorine resin laminate, plastic, bulk silicon or other macromolecules by means of commonly known methods, it is possible to prevent the rubber stopper from directly contacting the hGH solution, thereby suppressing the elution of metal ions from the rubber stopper. Rubber stoppers coated by means of such conventional methods should be evaluated by means of the test described in paragraphs (1)-(4), and selected under similar criteria for employment in the container of the present invention.

Unlike a rubber stopper for a vial, a plunger must use a material which is harder (there are usually more additives to the rubber) than that of a simple vial stopper due to the functional property of moving inside the cartridge during use and deciding the dosage delivered. While coatings by bulk silicon or the like which may be scraped off due to friction are not generally held to be preferable for surface treatment, it is possible to have a coating with only a small amount of silicon in order to reduce the friction. Therefore, the plunger which is suitable for carrying out the present invention must clear standards which are more stringent than those of a normal rubber stopper for vials. Specifically, the tests described in paragraphs (1)-(3) should be performed, and those with a zinc and/or aluminum ion concentration of 20 ppm or less should be used.

Herebelow, experiments performed on the rubber stoppers of the storage container shall be explained.

1) Method of Analysis

(i) Metal Ion Content

The quantitative analysis of metal ions in the solution was performed using atomic absorption spectrophotometry according to conventional methods.

(ii) hGH Content, Polymer Content

Size-exclusion chromatography was performed using a TSK G2000SWXL with 200 mM sodium phosphate (pH 6.8)/0.1% SDS/0.04% Polysorbate 20 as the mobile phase. The flow rate was 0.7 mL/min, and measured at 214 nm.

(ii) Deamidate Content

Anion exchange chromatography ((HPIEC) was performed using a TSK DEAE 3SW column (0.75 mm × 7.5 cm) at 40 °C with a flow rate of 1.0 mL/min. This column was equilibrated with a 25 mM bis-tris buffer (pH 5.8). Elution was performed using a 40 min gradient of 25 mM bis-tris buffer/0.5 M sodium chloride. Measurements were performed at 280 nm.

2) Experimental Method

(i) Experiment 1 Effects of Metal Ions on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle A solution in which was dissolved zinc acetate, aluminum chloride, calcium chloride and magnesium chloride was antiseptically added to the above-described sample so as to make the metal ion concentration a standard concentration, and the changes in the solubility state were observed.

(ii) Experiment 2 Elution of Metal Ions from Rubber Stopper

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 8 77 mg of sodium chloride, 2 5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each rubber stopper (rubber stopper B1 of Company B and rubber stoppers A1, A2, A3 and A4 of Company A) was immersed in the above-described sample, which was then stored at room temperature while shaking for a week. Thereafter, the metal ion concentration in the solution was measured.

(iii) Experiment 3 Effects of Rubber Stopper on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. A rubber stopper (rubber stopper B1 of Company B) with a high metal ion elution rate was immersed in the above-described sample, and 200 ppm of 2-sodium ethylene diamine 4-acetate was added. The change in the solubilization state was observed after letting stand at room temperature for 1 week

(iv) Experiment 4 Effects of Various Rubber Stoppers on hGH

1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each type of rubber stopper was immersed in the hGH solution. The pH change, content change, deamidate content and polymer content were measured after storing the prepared samples for one month under 5 °C and 25 °C conditions

3) Experiment Results

(i) Experiment 1 Effects of Metal Ions on hGH

With regard to zinc ions and aluminum ions, nebulation was observed in samples wherein 100 ppm and 50 ppm were respectively added. On the other hand, there was no nebulation in the samples into which magnesium ions and calcium ions

were added (Table 1).

Table 1

Metal Ion	Conc Added	0 ppm	20 ppm	50 ppm	100 ppm
Zn^{2+}	Property pH	clear 6.06	clear	clear 6.00	nebulation 5.97
Al^{3+}	Property pH	clear 6.03	clear	nebulation 5.82	nebulation 5.58
Mg^{2+}	Property pH	clear 6 08	clear	clear	clear
Ca^{2+}	Property pH	clear 6.05	clear	clear	clear

(ii) Experiment 2 Elution of Metal Ions from Rubber Stopper

With the rubber stopper B1 of Company B, the rate of elution of aluminum ions was considerably higher than in other rubber stoppers (Table 2).

Table 2

Rubber Stopper	Zn^{2+}	Al^{3+}	Mg^{2+}	Ca^{2+}
B1	82.7	2.5	0.2	0.0
A1	0 4	0.2	0.4	0 0
A2*	0.3	0 0	0.1	0 0
A3*	17.3	1 5	0.4	0 0
A4*	3 9	1 1	0.1	0.0

Note. elution units. ppm/unit
rubber stoppers weights approximately 850 mg/unit
*rubber stoppers weigh approximately 240 mg/unit

(iii) Experiment 3 Effects of Rubber Stoppers on hGH

The samples in which the rubber stopper B1 of company B were immersed were observed to have nebulation during storage However, the sample in which a rubber stopper B1 of Company B was immersed after adding the chelating agent 2-sodium ethylene diamine 4-acetate was not observed to have nebulation (Table 3)

Table 3

	No Rubber Stopper	Rubber Stopper Present*
EDTA 0 ppm	clear	nebulation
EDTA 200 ppm	clear	clear

* rubber stopper B1 of Company B

After one week of stationary storage at room temperature

(iv) Experiment 4 Effects of Various Rubber Stoppers on hGH

Nebulation was observed during storage of a sample in which the rubber stopper B1 of Company B was immersed, and a drop in content was confirmed (25 °C for 1 month) Additionally, in the samples in which the rubber stopper B1 of Company B was immersed, the pH of the solution rose and there was considerable generation of deamidates and polymer content.

Table 4

Rubber Stopper	Storage Conditions	pH	Solubility State	hGH Content[1)]	Deamidate Content[2)]	Polymer Content
B1	5 °C for 1M	6.72	clear	100%	2 8%	0.8%
	25 °C for 1M	7 75	nebulation	81%	20.5%	10.4%
A3	5 °C for 1M	6.17	clear	99%	2.8%	0.3%
	25 °C for 1M	6.30	clear	102%	10 7%	1 0%
A4	5 °C for 1M	6.20	clear	99%	3.0%	0.3%
	25 °C for 1M	6 41	clear	101%	11.7%	0 6%
A1	5 °C for 1M	6 15	clear	100%	3.0%	0.2%
	25 °C for 1M	6 21	clear	100%	10 7%	0 5%
None	5 °C for 1M	6 08	clear	100%	3 2%	0 4%

1) The hGH content was calculated with the sample content after storage at 5 °C for 1M without a stopper as 100%.

2) The deamidate content includes cyclic imides

CLAIMS

1. A storage container for a weakly acidic solution formulation containing human growth hormone, comprising:

a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening;

a first sealing member for sealing said first opening; and

a second sealing member provided in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with said first sealing member for containing the weakly acidic solution formulation containing human growth hormone;

said storage container for a weakly acidic solution formulation containing human growth hormone being characterized in that:

said second sealing member is composed of a type of rubber such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6 5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

2. A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein said first sealing member is composed of a type of rubber such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

3. A storage container for a weakly acidic solution formulation in accordance with either claim 1 or 2, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4 A storage container for a weakly acidic solution formulation in accordance with any one of claims 1-3, wherein said polyvalent metal ions are zinc ions or aluminum ions

5. An injection cartridge for a weakly acidic solution formulation containing

human growth hormone, comprising:

a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening,

a first sealing member for sealing said first opening, having a thickness such as to be capable of being punctured by a syringe needle; and

a second sealing member provided in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with said first sealing member for containing the weakly acidic solution formulation containing human growth hormone;

said injection cartridge for a weakly acidic solution formulation containing human growth hormone being characterized in that:

said second sealing member is composed of a type of rubber such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

6 An injection cartridge for a weakly acidic solution formulation containing human growth hormone in accordance with claim 5, wherein said first sealing member is composed of a type of rubber such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

7 A method for storing a weakly acidic solution containing human growth hormone, comprising steps of:

preparing a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening,

providing a rubber stopper in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming a space with said first sealing member;

filling said space with the weakly acidic solution formulation containing human growth hormone; and

sealing said first opening with a cap;

said method for storing a weakly acidic solution containing human growth hormone being characterized in that said rubber stopper is composed of a type of rubber such that after such a rubber stopper is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

8. A method for storing a weakly acidic solution containing human growth hormone in accordance with claim 7, comprising a step of adding a polyvalent metal ion chelating agent to the weakly acidic solution containing human growth hormone.

9. A sealing member for a storage container for a weakly acidic solution formulation, the sealing member comprising

a type of rubber such that after the sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5 5-6 5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

10. The sealing member of claim 9 wherein the elution rate of said polyvalent metal ions is 20 ppm or less

11. The sealing member of claim 9 wherein said polyvalent metal ions are zinc ions or aluminum ions.

12. A process for determining whether a sealing member is suitable for use in a storage container for a weakly acidic solution formulation containing human growth hormone, the process comprising the steps of:

(a) immersing the sealing member in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5;

(b) storing the immersed sealing member at a temperature of 25 °C for 1 week;

(c) simultaneously with step (b) shaking the immersed sealing member at a temperature of 25 °C for 1 week; and

(d) measuring the elution rate of polyvalent metal ions in said buffer

solution.

13. The process of claim 12 wherein step (d) is performed by atomic absorption spectrophotometry.

14. The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 50 ppm or less.

15 The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 20 ppm or less

16. The process of claim 12 further comprising a step (e) of adding a polyvalent metal ion chelating agent to the weakly acidic solution containing human growth hormone.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61M 5/315

A1

(11) International Publication Number: WO 00/59562

(43) International Publication Date: 12 October 2000 (12.10.00)

(21) International Application Number: PCT/IB00/00608

(22) International Filing Date: 31 March 2000 (31.03.00)

(30) Priority Data:
11/96443 2 April 1999 (02.04.99) JP

(71) Applicant *(for all designated States except US)*: SUMITOMO PHARMACEUTICALS, K.K. [JP/JP]; 2–8 Doshomachi 2–chome, Chuo–ku, Osaka 541–8510 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MORITA, Shigetoshi [JP/JP]; Kouyou–cho Naka 2–Chome, 1–Ban 214–1322, Higashinada–ku, Koube City 658–0032 (JP). TANAKA, Katsumi [JP/JP]; Tamagawa 1–Chome 9–1 #110, Takatsuki City, Osaka–ku 569–0857 (JP). YOSHIMOTO, Atsushi [JP/JP]; Hukui–cho 12–18, Takarazuka City, Hyougo Prefc. 665–0046 (JP).

(74) Agent: SONODA, Yoshitaka; Sonoda & Kobayashi, 4F/W1, Time–24 Building, 2–45 Aomi, Koto–ku, Tokyo 135–8073 (JP).

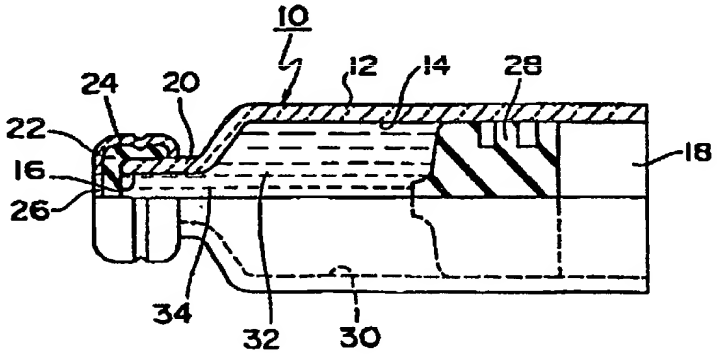
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR

(57) Abstract

The invention has the purpose of offering a storage container wherein flocculation and nebulation of hGH does not occur during storage of an hGH solution. A rubber stopper is formed of rubber such that when one such rubber stopper is immersed in 1ml of a buffer solution having a pH of approximately 5.5 to 6.5 and containing a surfactant, stored while shaking for one week at a temperature of 25 °C, then the metal ion elution rate in the buffer solution is measured using atomic absorption spectrophotometry, the elution rate of polyvalent metal ions is 50 ppm or less.



Inventor MORITA et al
Docket No . 11669 99USWO
Title STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR
Attorney Name Natalie D Kadievitch
Phone No 612 336 4706
Sheet 1 of 1

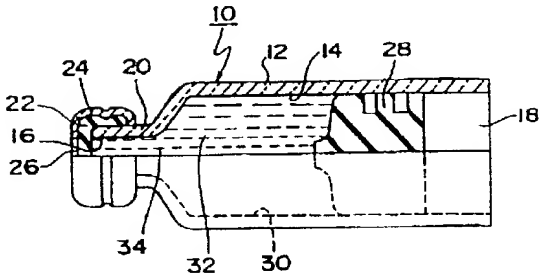


FIG. 1

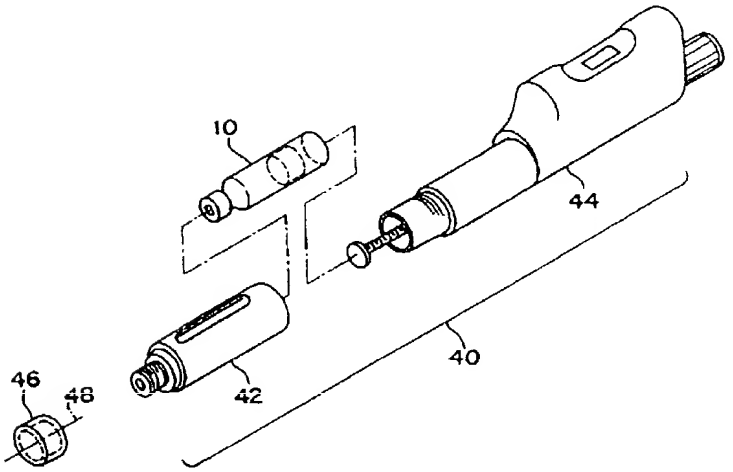


FIG. 2

Attorney Docket No. 11669.99USWO

MERCHANT & GOULD P.C.

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

The specification of which
a. ☐ is attached hereto
b. ☒ was filed on 25 September 2001 as application serial no. and was amended on (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/IB00/00608 filed 31 March 2000 and as amended on (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☐ no such applications have been filed.
b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**
Japan	11/96443	2 April 1999	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

U.S. PROVISIONAL APPLICATION NUMBER	DATE OF FILING (Day, Month, Year)

I acknowledge the duty to disclose information that is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (reprinted below):

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

(e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Albrecht, John W.	Reg. No. 40,481	Larson, James A.	Reg. No. 40,443
Ali, M. Jeffer	Reg. No. 46,359	Leonard, Christopher J.	Reg. No. 41,940
Altera, Allan G.	Reg. No. 40,274	Liepa, Mara E.	Reg. No. 40,066
Anderson, Gregg I.	Reg. No. 28,828	Lindquist, Timothy A.	Reg. No. 40,701
Batzli, Brian H.	Reg. No. 32,960	Lown, Jean A.	Reg. No. P-48,428
Beard, John L.	Reg. No. 27,612	Mayfield, Denise L.	Reg. No. 33,732
Berns, John M.	Reg. No. 43,496	McDonald, Daniel W.	Reg. No. 32,044
Branch, John W.	Reg. No. 41,633	McIntyre, Jr., William F.	Reg. No. 44,921
Bremer, Dennis C.	Reg. No. 40,528	Mitchem, M. Todd	Reg. No. 40,731
Brown, Jeffrey C.	Reg. No. 41,643	Mueller, Douglas P.	Reg. No. 30,300
Bruess, Steven C.	Reg. No. 34,130	Nelson, Anna M.	Reg No. P-48,935
Byrne, Linda M.	Reg. No. 32,404	Parsons, Nancy J.	Reg. No. 40,364
Campbell, Keith	Reg. No. 46,597	Pauly, Daniel M.	Reg. No. 40,123
Carlson, Alan G.	Reg. No. 25,959	Phillips, John B.	Reg. No. 37,206
Caspers, Philip P.	Reg. No. 33,227	Pino, Mark J.	Reg. No. 43,858
Clifford, John A.	Reg. No. 30,247	Prendergast, Paul	Reg. No. 46,068
Cook, Jeffrey	Reg. No. P-48,649	Pytel, Melissa J.	Reg. No. 41,512
Daignault, Ronald A.	Reg. No. 25,968	Qualey, Terry	Reg. No. 25,148
Daley, Dennis R.	Reg. No. 34,994	Reich, John C.	Reg. No. 37,703
Dalglish, Leslie E.	Reg. No. 40,579	Reiland, Earl D.	Reg. No. 25,767
Daulton, Julie R.	Reg. No. 36,414	Samuels, Lisa A.	Reg. No. 43,080
DeVries Smith, Katherine M.	Reg. No. 42,157	Schmaltz, David G.	Reg. No. 39,828
DiPietro, Mark J.	Reg. No. 28,707	Schuman, Mark D.	Reg. No. 31,197
Doscotch, Matthew A.	Reg No. P-48,957	Schumann, Michael D.	Reg. No. 30,422
Edell, Robert T.	Reg. No. 20,187	Scull, Timothy B.	Reg. No. 42,137
Epp Ryan, Sandra	Reg. No. 39,667	Sebald, Gregory A.	Reg. No. 33,280
Glance, Robert J.	Reg. No. 40,620	Skoog, Mark T.	Reg. No. 40,178
Goggin, Matthew J.	Reg. No. 44,125	Spellman, Steven J.	Reg. No. 45,124
Golla, Charles E.	Reg. No. 26,896	Stewart, Alan R.	Reg. No. 47,974
Gorman, Alan G.	Reg. No. 38,472	Stoll-DeBell, Kirstin L.	Reg. No. 43,164
Gould, John D.	Reg. No. 18,223	Sullivan, Timothy	Reg. No. 47,981
Gregson, Richard	Reg. No. 41,804	Sumner, John P.	Reg. No. 29,114
Gresens, John J.	Reg. No. 33,112	Swenson, Erik G.	Reg. No. 45,147
Hamer, Samuel A.	Reg. No. 46,754	Tellekson, David K.	Reg. No. 32,314
Hamre, Curtis B.	Reg. No. 29,165	Trembath, Jon R.	Reg. No. 38,344
Harrison, Kevin C.	Reg. No. 46,759	Tunheim, Marcia A.	Reg. No. 42,189
Hertzberg, Brett A.	Reg. No. 42,660	Underhill, Albert L.	Reg. No. 27,403
Hillson, Randall A.	Reg. No. 31,838	Vandenburgh, J. Derek	Reg. No. 32,179
Holzer, Jr., Richard J.	Reg. No. 42,668	Wahl, John R.	Reg. No. 33,044
Hope, Leonard J.	Reg. No. 44,774	Weaver, Paul L.	Reg. No. P-48,640
Jardine, John S.	Reg. No. P-48,835	Welter, Paul A.	Reg. No. 20,890
Johnston, Scott W.	Reg. No. 39,721	Whipps, Brian	Reg. No. 43,261
Kadievitch, Natalie D.	Reg. No. 34,196	Whitaker, John E.	Reg. No. 42,222
Kaseburg, Frederick A.	Reg. No. 47,695	Wier, David D.	Reg. No. P-48,229
Kettelberger, Denise	Reg. No. 33,924	Williams, Douglas J.	Reg. No. 27,054
Keys, Jeramie J.	Reg. No. 42,724	Withers, James D.	Reg. No. 40,376
Knearl, Homer L.	Reg. No. 21,197	Witt, Jonelle	Reg. No. 41,980
Kowalchyk, Alan W.	Reg. No. 31,535	Wu, Tong	Reg. No. 43,361
Kowalchyk, Katherine M.	Reg. No. 36,848	Young, Thomas	Reg. No. 25,796
Lacy, Paul E.	Reg. No. 38,946	Zeuli, Anthony R.	Reg. No. 45,255

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Merchant & Gould P.C. to the contrary. I understand that the execution of this document, and the grant of a power of attorney, does not in itself establish an attorney-client relationship between the undersigned and the law firm Merchant & Gould P.C., or any of its attorneys. Please direct all correspondence in this case to Merchant & Gould P.C. at the address indicated below:

Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

*2355
2*

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-02	**Full Name Of Inventor**	**Family Name** MORITA	**First Given Name** Shigetoshi	**Second Given Name**
0	**Residence & Citizenship**	**City** Koube City	**State or Foreign Country** Japan JPX	**Country of Citizenship** Japan
1	**Mailing Address**	**Address** Kouyou-cho, Naka 2-Chome, 1-Ban 214-1322	**City** Koube City	**State & Zip Code/Country** Higashinada-ku, 658-0032, Japan
Signature of Inventor 201: S. Morita			**Date:** 16 April, 2002	
2-02	**Full Name Of Inventor**	**Family Name** TANAKA	**First Given Name** Katsumi	**Second Given Name**
0	**Residence & Citizenship**	**City** Takatsuki City	**State or Foreign Country** Japan JPX	**Country of Citizenship** Japan
2	**Mailing Address**	**Address** Tamagawa 1-Chome 9-1 #110	**City** Takatsuki City	**State & Zip Code/Country** Osaka-fu 569-0857, Japan
Signature of Inventor 202: Katsumi Tanaka			**Date:** 16 April 2002.	
3-02	**Full Name Of Inventor**	**Family Name** YOSHIMOTO	**First Given Name** Atsushi	**Second Given Name**
0	**Residence & Citizenship**	**City** Takarazuka City	**State or Foreign Country** Japan JPX	**Country of Citizenship** Japan
3	**Mailing Address**	**Address** Hukui-cho 12-18	**City** Takarazuka City	**State & Zip Code/Country** Hyougo Prefc. 665-0046, Japan
Signature of Inventor 203: Atsushi Yoshimoto			**Date:** 16 April, 2002.	